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ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/090,879	SOMERS ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,30-32,34,35,37,39,40 and 42-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,30-32,34,35,37,39,40 and 42-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 October 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/15/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A sequence alignment*.

DETAILED ACTION

Status of the Application

[1] Claims 1, 3-4, 6, 30-32, 34-35, 37, 39-40, and 42-54 are pending in the application.

[2] Applicant's amendment to the claims, filed on 9/15/08, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 9/15/08, is acknowledged.

[4] Receipt of an information disclosure statement, filed on 9/15/08, is acknowledged.

[5] Receipt of a sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, a statement that no new matter has been added to the specification by the paper copy of the sequence CRF, and an amendment directing entry of the substitute sequence listing paper copy into the specification, all filed on 9/15/08, is acknowledged.

[6] Applicant's arguments filed on 9/15/08 in response to the Office action mailed on 3/14/08 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

[8] All references cited in the IDS filed on 9/15/08 have been considered by the examiner. A copy of Forms PTO-1449 is attached to the instant Office action.

[9] References C2 (Somers et al.) and E2 (Tonetti et al.) have been lined through as the references has already been made of record in the Form PTO-892 mailed on 3/14/08.

Claim for Domestic Priority

[10] Applicant's claim to domestic priority under 35 U.S.C. 121 to US non-provisional application 09/373,432, filed on 8/13/99, is acknowledged. Applicant's claim to domestic priority under 35 U.S.C. 119(e) to US provisional application 60/096,452, filed on 8/13/98, is acknowledged. The priority claim has been updated in the specification amendment filed on 9/15/08.

[11] Applicant states that this application is a continuation or divisional application of the prior-filed application. A continuation or divisional application cannot include new matter. Applicant is required to change the relationship (continuation or divisional application) to continuation-in-part because this application contains the matter not disclosed in the prior-filed application as described in the new matter rejection under 35 U.S.C. 112, first paragraph, below. See also MPEP 602.05.(a), which states, "[i]f the examiner determines that the continuation or divisional application contains new matter relative to the prior application, the examiner should so notify the applicant in the next Office action. The examiner should also *>(A)< require a new oath or declaration along

with the surcharge set forth in 37 CFR 1.16*>(f)<; and *>(B)< indicate that the application should be redesignated as a continuation-in-part."

Specification/Informalities

[12] The drawing figures filed on 10/29/04 are not properly labeled in accordance with 37 CFR 1.84(u)(1), which states, "Partial views intended to form one complete view, on one or several sheets, must be identified by the same number followed by a capital letter." Appropriate correction is required.

[13] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Crystal of an *Escherichia coli* GDP-Fucose Synthetase Polypeptide---.

RESPONSE TO ARGUMENT: At p. 172 of the instant remarks, applicant states the figures have been corrected and the specification title has been amended. However, the examiner can find no drawing correction and/or amendment to the title of the specification in the response filed on 9/15/08.

Claim Objection

[14] Claim 37 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 37 is dependent

upon claim 35, which already requires the active site to comprise amino acids Ser107, Tyr136, and Lys140 and thus does not further limit claim 35.

Claim Rejections - 35 USC § 112, Second Paragraph

[15] Claim(s) 44-45 and 50-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation of "crystal comprises the structural coordinates" as a skilled artisan would recognize that a crystal does not comprise structural coordinates. Instead, a crystal diffracts x-rays to produce a diffraction pattern, which is used to determine structural coordinates of a polypeptide. It is suggested that applicant clarify the meaning of the noted phrase.

[16] The rejection of claims 44-45 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "Protein Databank entry code 1GFS" in claim 44 and "Protein Databank entry code 1FXS or 1BSV" in claim 45 is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See paragraph 17, part h, beginning at p. 7 of the Office action mailed on 3/14/08. Newly added claims 50-52, also reciting PDB entry codes, have been included in the instant rejection. Thus, claims 44-45 and 50-52 are rejected herein.

RESPONSE TO ARGUMENT: At p. 174 of the instant remarks, applicant states "To clarify the meaning of these claims, the specification has been amended to incorporate the deposited coordinates".

Applicant's amendment to the specification to add the structural coordinates of each of PDB accession codes 1GFS, 1FXS, and 1BSV is acknowledged. Since the structural coordinates of PDB accession codes 1GFS, 1FXS, and 1BSV have now been added to the specification and since it appears to essential to the claimed invention, the claims should refer to the coordinates of the specification, rather than PDB accession codes 1GFS, 1FXS, and 1BSV. See MPEP 2172.01.

Claim Rejections – 35 USC § 112, First Paragraph

[17] The new matter rejection of claims 31-32, 34, 40, and 43-45 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 18 beginning at p. 8 of the Office action mailed on 3/14/08. Claims 1, 3-4, 6, 30, 35, 37, 39, 42, and 46-54 are included in the rejection for reasons noted below. Thus, claims 1, 3-4, 6, 30-32, 34-35, 37, 39-40, and 42-54 are rejected herein.

RESPONSE TO ARGUMENT: Beginning at p. 175 of the instant remarks, applicant argues the rejection is obviated by amendment to the claims. However, at least for the reasons set forth above, it is the examiner's position that the specification fails to provide adequate descriptive support for the claimed crystals.

Applicant's argument is not found persuasive. The only apparent descriptive support for the claimed crystals appears in the specification at pp. 21-24, which describes the specific species of crystals as follows: 1) a crystalline *E. coli* GFS of SEQ ID NO:2 having unit cell parameters a=104.2 Å and c=74.9 Å and space group symmetry $P3_221$ or $P3_121$ (p. 21), deposited as PDB entry 1GFS (p. 24, middle); 2) a crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADP+ having unit cell parameters a=104.2 Å and c=75.1 Å and space group symmetry $P3_221$ (p. 24, middle), deposited as PDB entry 1FXS (p. 24, middle); and 3) a crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADPH having unit cell parameters a=104.3 Å and c=74.9 Å and space group symmetry $P3_221$ (p. 24, top), deposited as PDB entry 1FXS (p. 24, middle). However, the claims, by reciting one or more of – but not all of – sequence, space group, and/or unit cell dimensions, are broader than the specification's descriptive support.

It is acknowledged that claims 46-53 recite sequence, space group, and unit cell dimensions, however, it is noted that the unit cell parameters include a value for parameter b as being equal to 104.20 Å or 104.3 Å, which does not appear to be supported by the original application.

It is suggested that applicant show support for the limitations at issue.

[18] The written description rejection of claims 1, 3-4, 6, 30-32, 34-35, 37, 39-40, and 42-45 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action.

See particularly paragraph 19 beginning at p. 10 of the Office action mailed on 3/14/08. Claims 46-54 are included in the rejection for reasons noted below. Thus, claims 1, 3-4, 6, 30-32, 34-35, 37, 39-40, and 42-54 are rejected herein.

RESPONSE TO ARGUMENT: Beginning at p. 176 of the instant remarks, applicant argues the rejection is obviated by amendment to the claims, the specification's disclosed representative species, and in view of hypothetical claim 1 of case 4 of the Trilateral Report on 3D structure related claims.

Applicant's argument is not found persuasive. The examiner acknowledges applicant's amendment to the claims, which requires a crystal having *inter alia* unit cell parameters (claim 1), GFS sequence, ligand, and space group (claims 6), GFS sequence, space group, and unit cell dimensions (claim 46), and GFS sequence and space group (claim 54). The examiner further acknowledges the specification's 3 disclosed representative species and hypothetical claim 1 of case 4 of the Trilateral Report on 3D structure related claim. However, the examiner maintains the position that the specification fails to adequately describe the claimed crystals.

As noted in the prior Office action, it was well-known at the time of the invention that protein crystallography was a highly unpredictable art. See, *e.g.,* the teachings of McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990), which states (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to

proteins that differ by no more than one or just a few amino acids." Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out, trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual." See also the cited teachings of, *e.g.,* Branden et al., Drenth et al., Kierzek et al., and Wiencek as set forth at pp. 16-19 of the Office action mailed on 3/14/08. That protein crystallography was highly unpredictable does not appear to be disputed by applicant.

Other than the 3 disclosed representative species, the specification fails to disclose any additional species of the genus of crystalline proteins, optionally in complex with NADP+ or NADPH, to achieve formation of a crystal having the recited characteristics. In other words, other than the 3 disclosed representative species, there is no disclosed correlation between the sequence of a GFS polypeptide, an optional

NADP+ or NADPH ligand that will achieve formation of a crystal having the recited characteristics as encompassed by the claims. As noted by Branden et al. (*supra*), "The formation of crystals is also critically dependent on a number of different parameters, including…added…legends to the protein" and McPherson points out that trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by "no more than one or just a few amino acids" can result in significant influences upon the change in which variables are important for successful crystallization. That structurally similar polypeptides do not form crystals with similar crystal structures is evidenced by Tonetti et al. (*Acta Crystallogr D Biol Crystallogr* 54:684-687, July 1998), which, according to applicant, teaches a crystal of an *E. coli* GFS whose sequence is different to that of SEQ ID NO:2 by only two additional C-terminal amino acids (instant remarks at p. 181), yet the crystal has a different space group and/or unit cell dimensions. See also the reference of Thoden et al. (*Biochemistry* 35:2557-2566, 1996; cited as reference D10 in the 9/15/08 IDS), which teaches a crystal of *E. coli* GFS that has unit cell dimensions that are different to that of the claimed crystal. That protein crystallography was highly unpredictable, even among proteins that are structurally similar with respect to their amino acid sequences does not appear to be disputed by applicant.

With respect to the Trilateral Report, it is noted that the hypothetical examples in the Trilateral Report are given to provide *guidance* with respect to patentability, they are not to be taken as a rigid test for patentability.

Given the high level of unpredictability associated with protein crystallography and the lack of description of a representative number of species to reflect the variation among members of the genus, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[19] The scope of enablement rejection of claims 1, 3-4, 6, 30-32, 34-35, 37, 39-40, and 42-45 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 20 beginning at p. 14 of the Office action mailed on 3/14/08. Claims 46-54 are included in the rejection for reasons noted below. Thus, claims 1, 3-4, 6, 30-32, 34-35, 37, 39-40, and 42-54 are rejected herein.

RESPONSE TO ARGUMENT: Beginning at p. 178 of the instant remarks, applicant argues the rejection is obviated by amendment to the claims, which are commensurate in scope with hypothetical claim 1 of case 4 of the Trilateral Report on 3D structure related claims, and the guidance and working examples provided in the specification.

Applicant's argument is not found persuasive. The examiner acknowledges applicant's amendment to the claims, which requires a crystal having *inter alia* unit cell parameters (claim 1), GFS sequence, ligand, and space group (claims 6), GFS sequence, space group, and unit cell dimensions (claim 46), and GFS sequence and space group (claim 54). The examiner further acknowledges the specification's 3

disclosed working examples and hypothetical claim 1 of case 4 of the Trilateral Report on 3D structure related claim. However, the examiner maintains the position that the specification fails to enable the full scope of the claimed crystals.

The broad scope of claimed crystals and crystallization methods is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to 1) a crystalline *E. coli* GFS SEQ ID NO:2 having unit cell parameters a=104.2 Å and c=74.9 Å and space group symmetry $P3_221$; 2) a crystalline *E. coli* GFS SEQ ID NO:2 in complex with NADP+ having unit cell parameters a=104.2 Å and c=75.1 Å and space group symmetry $P3_221$; and 3) a crystalline *E. coli* GFS SEQ ID NO:2 in complex with NADPH having unit cell parameters a=104.3 Å and c=74.9 Å and space group symmetry $P3_221$.

Although applicant argues that it would require no more than routine experimentation to make all crystals as encompassed by the claims, as noted in the prior Office action, the state of the art at the time of the invention acknowledges a high level of unpredictability for making a protein crystal with an expectation that the crystal will be of diffraction quality. The reference of Branden et al. teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals…are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict

a priori those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al., which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). In view of these teachings, there is no expectation that a skilled artisan can use the disclosed crystallization conditions to achieve diffraction quality crystals of other *E. coli* GFS polypeptides. Also, Wiencek teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units…some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). Additionally, Buts et al. teaches that "Since the introduction of structural genomics, the protein has been recognized as the most important variable in crystallization." "Five naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution." Specifically, the reference of Buts *et al.* teaches that the F17e-G and F17f-G adhesins differ in only one amino acid from the F17c-G adhesin, Arg21Ser and His36Tyr, respectively, and yet these proteins that are 99% identical in sequence resulted in different crystal forms with distinct diffraction properties (see Tables 1-3). See also the teachings of McPherson as set forth above. Applicant does not appear to dispute the objective evidence of these references.

Even though the skill in the art is extremely high, even for those that are graced by being assisted with the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot et al. *Cell. Mol. Life Sci*. 2004, 61: 525-536) and currently there are no directed methods which makes this process any easier or more predictable. Thus, each protein that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins.

The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see Weber, *Methods in Enzymology*, 1997, Vol. 276, pp. 13-22). At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a role in obtaining crystallization conditions despite the extremely high skill level of those in the art (see Drenth, *supra,* Cudney, *Rigaku Journal*, 1999, Vol. 16, No. 1, pp. 1-7).

When these teachings are taken as a whole, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other *E. coli* GFS polypeptides optionally in complex with NADP+ OR NADPH having a desired space group and unit cell dimensions as encompassed by the claims can be achieved using the disclosed crystallization parameters as encompassed by the claims. That structurally similar polypeptides do not form crystals with the recited characteristic(s) is evidenced by Tonetti et al. (*Acta Crystallogr D Biol Crystallogr* 54:684-687, July 1998), which, according to applicant, teaches a crystal of an *E. coli* GFS whose sequence is different to that of SEQ ID NO:2 by only two additional C-terminal amino acids (instant remarks at p. 181), yet the crystal has a different space group and/or unit cell dimensions. See also the reference of Thoden et al. (*Biochemistry* 35:2557-2566, 1996; cited as reference D10 in the 9/15/08 IDS), which teaches a crystal of *E. coli* GFS that has unit cell dimensions that are different to that of the claimed crystal.

With respect to the Trilateral Report, it is noted that the hypothetical examples in the Trilateral Report are given to provide *guidance* with respect to patentability, they are not to be taken as a rigid test for patentability.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary

skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections – 35 USC § 102

[20] The rejection of claims 1-3, 5, 35, and 37 under 35 U.S.C. 102(a) as being anticipated by Tonetti et al. (*Acta Crystallogr D Biol Crystallogr* 54:684-687, July 1998); the rejection of claim 31 under 35 U.S.C. 102(b) as being anticipated by Tonetti; and the rejection of claim 38 is rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as being obvious over Tonetti are withdrawn in view of the instant claim amendment. The crystal of Tonetti is disclosed as having space group $P3_121$ and unit cell dimensions a=b=105.0 Å, c=75.6 Å, and $\gamma=120^{o}$ (p. 685, column 2). Also, the *E. coli* GFS of the crystal of Tonetti (p. 684, Figure 1 and p. 685, column 1) differs from SEQ ID NO:2 herein (see Appendix A sequence alignment) and is uncomplexed, *i.e.,* without ligand. The crystal of claims 1, 3-4, 30-32, 34-35, 37, and 44-53 is distinguished over Tonetti at least by requiring unit cell dimensions that are not taught or suggested by Tonetti. The crystal of claims 6, 39-40, 42-43, and 46-53 is distinguished over Tonetti at least by requiring a space group that is not taught or

suggested by Tonetti. The crystal of claim 54 is distinguished over Tonetti at least by requiring an *E. coli* GFS sequence that is not taught or suggested by Tonetti.

[21] Claims 1, 3-4, 6, 30-32, 34-35, 37, 39-40, and 42-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Somers et al. (*Structure* 6:1601-1612, December 1998; "Somers"). The claims are drawn to crystalline *E. coli* GFS having the limitations as recited therein.

Somers teaches a crystal of native recombinant *E. coli* GDP-fucose synthetase having space group $P3_221$ or $P3_121$ with unit cell parameters of a = 104.2 Å and c = 74.9 Å (p. 1609, column 1, middle) that diffracts x-rays to a resolution of 2.2 Å (p. 1609, Table 1, under *Native*). Somers further teaches a crystal of *E. coli* GDP-fucose synthetase in complex with NADP+ with unit cell parameters of a = 104.2 Å and c = 75.1 Å (p. 1609, column 2, middle) and a crystal of recombinant *E. coli* GDP-fucose synthetase in complex with NADPH with unit cell parameters of a = 104.3 Å and c = 74.9 Å (p. 1619, paragraph bridging columns 1-2). According to Somers, the structural coordinates for the GDP-fucose synthetase polypeptides have PDB entry accession codes 1GFS, 1FXS, and 1BSV (p. 1610, column 2, bottom). Although Somers does not expressly teach the sequence of the *E. coli* GFS used in the crystallization, since the polypeptide of Somers was made by a method identical to that disclosed in the specification at p. 21, top and would thus inherently have the amino acid sequence of SEQ ID NO:2. Also, although Somers does not teach the unit cell parameter b value,

since the crystal was made using a polypeptide and method identical to that disclosed herein, the crystal of Somers would inherently have the same unit cell parameters.

This anticipates claims 1, 3-4, 6, 30-32, 34-35, 37, 39-40, and 42-54 as written.

RESPONSE TO ARGUMENT: Beginning at p. 182 of the instant remarks, applicant argues the claimed invention is entitled to a priority date of 8/13/98, pointing to pp. 24 and 26-27 of provisional application 60/096,452 as allegedly showing support for the claim limitations.

Applicant's argument is not found persuasive. Applicant's noted support in the '452 provisional application describes the specific species of crystals as follows: 1) a crystalline *E. coli* GFS of SEQ ID NO:2 having unit cell parameters a=104.2 Å and c=74.9 Å and space group symmetry $P3_221$ or $P3_121$ (p. 21), deposited as PDB entry 1GFS (p. 24, middle); 2) a crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADP+ having unit cell parameters a=104.2 Å and c=75.1 Å and space group symmetry $P3_221$ (p. 24, middle), deposited as PDB entry 1FXS (p. 24, middle); and 3) a crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADPH having unit cell parameters a=104.3 Å and c=74.9 Å and space group symmetry $P3_221$ (p. 24, top), deposited as PDB entry 1FXS (p. 24, middle). However, the claims, by reciting one or more of – but not all of – sequence, space group, and/or unit cell dimensions, are broader than the specification's descriptive support and thus are accorded a priority date of 3/4/02. As such, the reference of Somers is available as prior art under 35 U.S.C. 102(b).

Conclusion

[22] Status of the claims:

Claims 1, 3-4, 6, 30-32, 34-35, 37, 39-40, and 42-54 are pending.

Claims 1, 3-4, 6, 30-32, 34-35, 37, 39-40, and 42-54 are rejected.

No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
Primary Examiner, Art Unit 1656

APPENDIX A

Query sequence 1

>GENPEPT ACCESSION NUMBER P32055 (TONETTI)
MSKQRVFIAGHRGMVGSAIRRQLEQRGDVELVLRTRDELNLLDSRAVHDFFASERIDQVY
LAAAKVGGIVANNTYPADFIYQNMMIESNIIHAAHQNDVNKLLFLGSSCIYPKLAKQPMA
ESELLQGTLEPTNEPYAIAKIAGIKLCESYNRQYGRDYRSVMPTNLYGPHDNFHPSNSHV
IPALLRRFHEATAQNAPDVVVWGSGTPMREFLHVDDMAAASIHVMELAHEVWLENTQPML
SHINVGTGVDCTIRELAQTIAKVVGYKGRVVFDASKPDGTPRKLLDVTRLHQLGWYHEIS
LEAGLASTYQWFLENQDRFRG

Query sequence 2

>SEQ ID NO:2
KQRVFIAGHRGMVGSAIRRQLEQRGDVELVLRTRDELNLLDSRAVHDFFASERIDQVYLA
AAKVGGIVANNTYPADFIYQNMMIESNIIHAAHQNDVNKLLFLGSSCIYPKLAKQPMAES
ELLQGTLEPTNEPYAIAKIAGIKLCESYNRQYGRDYRSVMPTNLYGPHDNFHPSNSHVIP
ALLRRFHEATAQNAPDVVVWGSGTPMREFLHVDDMAAASIHVMELAHEVWLENTQPMLSH
INVGTGVDCTIRELAQTIAKVVGYKGRVVFDASKPDGTPRKLLDVTRLHQLGWYHEISLE
AGLASTYQWFLENQDRF

Full-length alignment between two sequences

>>SEQ ID NO:2 (317 aa)
 s-w opt: 2119 Z-score: 2601.2 bits: 489.5 E(): 4.5e-143
Smith-Waterman score: 2119; 100.000% identity (100.000% ungapped) in 317 aa overlap (3-319:1-317)

```
               10        20        30        40        50        60
GENPEP MSKQRVFIAGHRGMVGSAIRRQLEQRGDVELVLRTRDELNLLDSRAVHDFFASERIDQVY
         ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ      KQRVFIAGHRGMVGSAIRRQLEQRGDVELVLRTRDELNLLDSRAVHDFFASERIDQVY
                10        20        30        40        50

               70        80        90       100       110       120
GENPEP LAAAKVGGIVANNTYPADFIYQNMMIESNIIHAAHQNDVNKLLFLGSSCIYPKLAKQPMA
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ    LAAAKVGGIVANNTYPADFIYQNMMIESNIIHAAHQNDVNKLLFLGSSCIYPKLAKQPMA
       60        70        80        90       100       110

              130       140       150       160       170       180
GENPEP ESELLQGTLEPTNEPYAIAKIAGIKLCESYNRQYGRDYRSVMPTNLYGPHDNFHPSNSHV
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ    ESELLQGTLEPTNEPYAIAKIAGIKLCESYNRQYGRDYRSVMPTNLYGPHDNFHPSNSHV
      120       130       140       150       160       170

              190       200       210       220       230       240
GENPEP IPALLRRFHEATAQNAPDVVVWGSGTPMREFLHVDDMAAASIHVMELAHEVWLENTQPML
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ    IPALLRRFHEATAQNAPDVVVWGSGTPMREFLHVDDMAAASIHVMELAHEVWLENTQPML
      180       190       200       210       220       230

              250       260       270       280       290       300
GENPEP SHINVGTGVDCTIRELAQTIAKVVGYKGRVVFDASKPDGTPRKLLDVTRLHQLGWYHEIS
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ    SHINVGTGVDCTIRELAQTIAKVVGYKGRVVFDASKPDGTPRKLLDVTRLHQLGWYHEIS
      240       250       260       270       280       290

              310       320
```

```
GENPEP LEAGLASTYQWFLENQDRFRG
       ::::::::::::::::::
SEQ    LEAGLASTYQWFLENQDRF
      300       310
```